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# Evaluating the benefits of patterned stimulation in the treatment of osteoarthritis of the knee[1]

## A multi-center, randomized, single-blind, controlled study with an independent masked evaluator

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### Summary

*Objective*: This study investigated the benefits of the combination of interferential (IF) and patterned muscle stimulation in the treatment of osteoarthritis (OA) of the knee.

*Design*: This was a multi-center, randomized, single-blind, controlled study with an independent observer. The study randomized 116 patients with OA of the knee to a test or control group. The test group received 15 min of IF stimulation followed by 20 min of patterned muscle stimulation. The control group received 35 min of low-current transcutaneous electrical nerve stimulation (TENS). Both groups were treated for 8 weeks. Subjects completed questionnaires at baseline and after 2, 4 and 8 weeks. Primary outcomes included the pain and physical function subscales of the Western Ontario MacMaster (WOMAC) OA Index and Visual Analog Scales (VAS) for pain and quality of life.

*Results*: Compared to the control group, the test group showed reduced pain and increased function. The test group showed a greater decrease in the WOMAC pain subscale ($P = 0.002$), function subscale ($P = 0.003$) and stiffness subscale ($P = 0.004$). More than 70% of the test group, compared to less than 50% of the control group, had at least a 20% reduction in the WOMAC pain subscale. When analyzing only patients who completed the study, the test group had a nominally significant greater decrease in overall pain VAS. No significant between-group differences were observed in incidence of adverse events.

*Conclusions*: In patients with OA of the knee, home-based patterned stimulation appears to be a promising therapy for relieving pain, decreasing stiffness, and increasing function.


*Key words*: Knee osteoarthritis, Pain, Electric stimulation.

## Introduction

Osteoarthritis (OA) of the knee is the most common type of arthritis. More than 10 million Americans have OA of the knee[1]. Most people affected are older than 45 years. Pathologic changes in OA involve the progressive breakdown of the articular cartilage within the joint[2]. The symptoms include pain, swelling, bone spur formation and decreased range of motion[3]. This causes disability and impairs patients' quality of life. Given the lack of a direct cure, treatments for OA of the knee mainly focus on relieving pain, reducing inflammation, decreasing stiffness, maintaining joint mobility, and preventing further deformity[4,5]. Prescription medicines such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and opioids are used for the relief of pain[6–8]. Intra-articular injections can achieve short-term pain relief by lubricating the joint[9]. Regular low-impact exercises as well as physical therapy help to maintain range of motion, muscle strength and general health[10,11]. Unfortunately, pain medicines can have undesirable side effects: many NSAIDs, such as aspirin, may cause gastrointestinal distress, and narcotic painkillers carry a risk of addiction. The benefits of exercise can be compromised by skeletal or muscle damage or injury, and injections give only temporary relief of pain. Therefore, it is necessary to explore additional treatments for OA of the knee to better manage pain, save pain medication, and restore knee function.

Electrical stimulation has been used for relief of pain for many years, and its medical function has been accepted since the gate control theory was introduced[12]. The purpose of this randomized controlled study was to investigate the benefits of patterned stimulation vs conventional transcutaneous electrical nerve stimulation (TENS) in the treatment of OA of the knee. The test group was treated with an interferential (IF) stimulation coupled with patterned muscle stimulation. The control group was treated with low-current

[1]This paper contains confidential information of RS Medical.

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TENS. Since IF stimulation could provide long-lasting pain relief, and patterned muscle stimulation could promote mobility and restore function, this two-step treatment has the potential to be a more efficient treatment modality for OA of the knee than single-step TENS stimulation.

## Materials and methods

### ETHICAL CONSIDERATIONS

The procedures followed were in accordance with the ethical standards of 21 CFR §50, 21 CFR §56, and ICH GCP.

### ENROLLMENT

Patients were recruited by self-selection (advertisements) and by referral from patient databases from four study sites in the United States. Of the 116 subjects, 32 were enrolled at an orthopedic clinic in Tucson, AZ; 41 were enrolled at a clinical research organization (CRO) in San Antonio, TX; 32 were enrolled at a CRO in Portland, OR; and 11 were enrolled at a CRO in Eugene, OR. Before taking part in the study, participants were asked to read and sign an informed consent form approved by the central Institutional Review Board (Quorum IRB, Seattle, WA). Patients who met all inclusion criteria and did not violate any exclusion criteria were enrolled.

Criteria for inclusion were as follows: (1) evidence of OA in more than one joint based on a physician's assessment of patient-reported symptoms and a differential diagnosis or radiographic evidence; (2) radiographic evidence indicative of cartilage remaining in the entire knee and no bone-on-bone contact within 6 months of enrollment; (3) OA pain present more days than not in the knee chosen to receive electrical stimulation, and the overall pain VAS rating $\geq$ 40 mm on a 100 mm line; (4) OA stiffness present more days than not in the knee chosen to receive electrical stimulation, and typically lasting less than 30 min; (5) agreement to follow the treatment plan and to use the stimulation device; (6) older than 18; (7) signing the informed consent form.

Exclusion criteria were as follows: (1) hypersensitivity to electrostimulation; (2) had intra-articular injections within 3 months to the knee to receive electrostimulation; (3) if taking medications (e.g., oral steroids, non-steroidal anti-inflammatories or acetaminophen), the dosage had not been stable for at least 3 months prior to enrollment; (4) if taking chondroprotective supplements (e.g., glucosamine and chondroitin sulfate), the dosage had not been stable for at least 3 months prior to enrollment; (5) had pathologic processes causing a structural defect in or instability of the knee at the knee to receive electrostimulation (e.g., congenital defects, anatomical or mechanical deformities, blunt trauma); (6) had cartilage-related surgery in the last 2 years; (7) was pregnant or intended to become pregnant; (8) had known current or remittent malignancy or cancer; (9) had implanted cardiac pacemaker or defibrillator; (10) had a body mass index (BMI) $>$ 45; (11) had serious or uncontrolled systemic illness such as autoimmune disease, rheumatoid arthritis, diabetes mellitus or renal failure; (12) concurrently used another electrical stimulation device for treatment of knee symptoms; (13) previously or concurrently used an RS Medical stimulation device; (14) was recently in another clinical trial for medical devices or biologic agents; (15) had a relationship other than medical with principal investigators and their staff; (16) had a relationship with another enrolled patient; (17) was unable to complete the study or the case report forms.

### STUDY DESIGN

This study was designed as a multi-center, randomized, single-blind, controlled study with an independent masked evaluator to test the efficacy of patterned stimulation in treatment of OA of the knee, whereby patients were to receive one of two types of stimulation – IF plus patterned stimulation (the test group) or low-current TENS (the control group). Patients were blinded to the study hypothesis. Clinicians blinded to stimulation group assignment acted as independent masked observers and evaluators. Subjects in both groups received a single session of 35-min unilateral electrical stimulation daily for 8 weeks.

The baseline assessment included demographic data, OA symptoms and prior treatments. Patients were also asked to answer questionnaires on pain, OA-specific functioning, global impact of OA on life, and medication regimen. After the baseline assessment, patients were issued an electrical stimulation unit and instructed in the proper use of the device. The first treatment session was done under supervision in the clinic, and the rest were self-administered at home.

Post-stimulation assessments were performed at 2, 4, and 8 weeks ($\pm$2 days) after baseline, and patients were asked to answer the same questionnaires. A usage screening was set within 2 days of completion of the second week of stimulation. Based on the usage information recorded on the device, patients who did not complete a minimum of 50% of treatments during the first 2-week period were dropped from the study and considered screen failures. The study was completed after the 8-week assessment.

### INTERVENTIONS

The device used to deliver the electrical stimulation was the RS-4i® Stimulator (RS Medical, 14001 SE First Street, Vancouver, WA). Stimulators were pre-programmed to deliver either IF plus patterned muscle stimulation or low-current TENS treatment. Two channels employing four reusable 2-inch diameter cutaneous electrode pads were placed over the thigh and back of the leg. For channel 1, one pad was placed over the vastus lateralis (positive) and one over the vastus medialis (negative), and for channel 2, one pad was placed over the proximal hamstrings (negative) and one over the distal hamstrings (positive).

The test group stimulation session consisted of 15 min of IF stimulation (step 1) followed by 20 min of patterned muscle stimulation (step 2). IF stimulation had a base frequency of 5000 hertz (Hz) and a pre-modulated beat frequency sweeping between 1 and 150 Hz. The electrode placement for the IF step was the same as the patterned muscle stimulation placement, and the IF was used primarily to decrease any discomfort that could possibly be experienced during the patterned muscle stimulation mode. During IF stimulation mode, patients were asked to increase the intensity until experiencing a gentle tingling feeling on skin, but not muscular contraction. The muscle stimulation was a tri-phasic stimulation pattern based on electromyographic output of the normal activation timing and pattern of the quadriceps and hamstrings during a high-level running activity. This pattern of stimulation was specifically programmed into the device for the investigation. The patterned muscle stimulation delivered 50 Hz impulses for 200 ms every 1500 ms. The waveform was a biphasic square wave with a fixed amplitude of 60 mA. Stimulation intensity was controlled by varying the pulse width, which in this study ranged between 3.39 $\mu$s and 102.2 $\mu$s. Comparing the output of most common muscle stimulators that have a fixed pulse width of 300 $\mu$s results in an equivalent amplitude range from 0.52 mA to 40.06 mA. The average output used by the subjects in the test group was 16.26 mA (the mode was 9.51 mA). Patients were instructed to increase the intensity until feeling a mild but comfortable muscular contraction, and after 5 min, to turn up the intensity to produce a moderate to strong contraction that could be tolerated without causing pain.

Each low-current TENS session consisted of 35 min of TENS. It was delivered as a biphasic square wave with a 0.2 Hz frequency and a fixed amplitude of 60 mA, with pulse width adjusted to provide a net output of 73 nC. Delivered across 300 $\mu$s, this is equivalent to a peak output of 0.5 mA. The stimulation might be perceived but would not produce a muscular contraction. Patients receiving low-current TENS were told the intensity was preset, and adjustments had no effect on the actual current.

### OBJECTIVES

The study tested the difference in subjects with OA of the knee from baseline to 8 weeks of treatment with patterned stimulation, compared to 8 weeks of treatment with low-current TENS. The study evaluated changes in pain, function, quality of life, use of breakthrough pain medication, adherence to the study protocol, and safety of electrical stimulation.

### OUTCOME MEASUREMENTS

The Western Ontario MacMaster (WOMAC) OA Index is a validated instrument designed specifically for the assessment of pain and function in OA of the knee or hip. The WOMAC used in this study was the Likert version 3.1 standardized with English for an American population, consisting of 24 self-administrated questions that were answered for each item on a 5-point Likert scale (none, mild, moderate, severe and extreme). It was reported as three separate subscales: pain, physical function, and stiffness. The WOMAC pain subscale had five questions scored 0–4 and was considered invalid if more than one item was missing; hence, it had a range of 0 (no pain) to 20 (maximal pain). In the event of a missing item, the remaining four items were averaged and then multiplied by five. The WOMAC function subscale had 17 questions scored 0–4 and was considered invalid if more than three items were missing. It had a range of 0 (maximal function) to 68 (minimal function). In the event of missing items, the remaining items were averaged and then multiplied by 17. The WOMAC stiffness subscale had two items scored 0–4 and was considered invalid if either was missing; hence it had a range from 0 (no stiffness) to 8 (maximal stiffness). In the event of a missing item, the score for the remaining item was multiplied by two.

Visual analog scale (VAS) lines were used for measuring overall pain intensity and global impact of OA on quality of life. The VAS line for overall pain rating was anchored at one end with "0" and the label "No Pain" and at the other end with "100" and the label "Worst Pain Imaginable". VAS ratings were provided for both knees. The VAS line for the quality of life rating was anchored at one end with "0" and labeled "Very Poor" and at the other

end with ''100'' and labeled ''Very Good''. Subjects were instructed to place a mark on the line to report the intensity or quality of the sensation being experienced.

### RANDOMIZATION

Subjects were assigned on an individual basis to the test group (IF plus patterned muscle stimulation) or to the test group (low-current TENS). They remained on the same allocation throughout the duration of their participation in the study. Unblinded study physicians (or their authorized unblinded delegates) dispensed study devices, programmed to deliver either IF plus patterned stimulation or low-current TENS, according to a sponsor-provided random digits table with corresponding study groups. Blinded researchers responsible for determining eligibility allocated the next available number on entry into the trial, and then each subject collected an appropriately programmed stimulator device from the unblinded physician or delegate.

### BLINDING

Although subjects were informed that two treatment conditions were being evaluated, they were not made aware of the hypotheses until their participation and debriefing in the study was complete. Study physicians and study coordinators responsible for evaluations and assessments were blinded to treatment group allocations. Clinicians responsible for dispensing study devices and instructing subjects on the use of study devices were unblinded but did not serve in any other capacity during the study. Subjects were instructed to direct all questions about the study device to these unblinded clinicians.

### STATISTICAL ANALYSES

For baseline comparisons, continuous variables were compared with Student's *t* test. Dichotomous variables were compared by Pearson's chi-square or Fisher's exact test if the expected number in any cell was less than five. Nominal categorical variables with greater than two response categories were tested by Pearson's chi-square.

### SAMPLE SIZE

The study was designed to have 80% power to detect a difference between the two treatment groups with an effect size [mean difference divided by the standard deviation (SD)] of 0.6. Based on these assumptions, 45 patients per treatment group were required. To allow for dropouts or patients with inadequate data, the planned enrollment was increased by one-third to 60 patients per treatment group.

### PRIMARY ENDPOINTS

Primary endpoints include the following: (1) change from baseline in the WOMAC pain subscale; (2) change from baseline in the WOMAC function subscale; (3) change from baseline in VAS overall pain rating; (4) change from baseline in VAS quality of life rating. Primary effectiveness analysis was restricted to patients who passed the 2-week usage screening and had at least one post-baseline visit. Patients who had no post-randomization assessment or were missing a baseline assessment for any primary variable were excluded from the analysis of that variable. Each primary endpoint was analyzed by an analysis of variance (ANOVA) that included the effects of treatment group, study center, and the corresponding baseline assessment. Since there were four co-primary endpoints, a Bonferroni correction was employed; hence, each co-primary endpoint was tested using a two-sided test at a significance level of 0.0125 (0.05/4). All results were shown as SAS LSMEANS adjusted for the variables in the model and two-sided 98.75% confidence intervals (CIs) on their difference.

As a secondary analysis of each of the primary endpoints, all baseline variables that were nominally statistically significantly different between treatment groups were added to the primary model to assess their impact. This was done by a stepwise regression in which at each step the baseline variable with the highest $P$ value was excluded until all baseline variables remaining in the model had a $P$ value $< 0.10$.

### SECONDARY ENDPOINTS

Secondary endpoints include the following: (1) mean change from baseline to each scheduled visit for each primary endpoint to demonstrate the time course of effect; (2) frequency of patients reporting 20% or more improvement for each of the primary outcomes; (3) change in WOMAC stiffness subscale after 8 weeks of stimulation; (4) use of breakthrough medication for pain; (5) adherence to treatment protocol; (6) safety of electrical stimulation. Continuous secondary endpoints were analyzed using the same statistical model described for the primary variables. Dichotomous endpoints were analyzed by a logistic regression that included the effects of treatment group, study center, and the corresponding baseline assessment. Results for continuous variables were shown as least squares means adjusted for the variables in the model and two-sided 95% CIs on their difference. Results for dichotomous variables were presented as odds ratios estimated from the logistic regression and their two-sided 95% CIs. All $P$ values are reported as two-sided nominal values.

Adverse events were recorded as the number and percentage of patients reporting each event. Comparisons were made between treatment groups in adverse event rates by Fisher's exact test.

All statistical analyses were completed using the SAS/STAT® software, version 9.1.

## Results

### PARTICIPANTS' PROGRESSION

From a pool of 136 individuals, a total of 116 met the screening criteria and were randomized (Fig. 1). Fifty-seven patients in the test group and 59 patients in the control group were given a baseline assessment. All 116 randomized patients were included in the safety analysis.

Seven patients (three in the test group and four in the control group) used the stimulation device for less than 50% of the days during the first 2-week period and were dropped from the study as screen failures. Therefore, these patients were excluded from all analyses of effectiveness. The remaining 109 patients (54 in the test group and 55 in the control group) were considered eligible for effectiveness analysis. Of the 109 patients, 106 (53 in each group) had at least one post-baseline visit and were included in the effectiveness analyses of primary endpoints.

Six patients (three in each group) dropped out of the study between the Week 2 and Week 4 assessments, and another two (one in each group) dropped out between the Week 4 and Week 8 assessments due to an adverse event, lack of effectiveness, loss to follow-up or patient decision. A total of 101 patients completed the 8-week study (Fig. 1).

### RECRUITMENT

Subject recruitment began on January 22, 2004. The first subject was enrolled on February 17, 2004, and the last subject was enrolled on March 1, 2005. The last subject completed participation in the study on April 25, 2005. Participants attended clinic visits at baseline and again after 2 weeks, 4 weeks, and 8 weeks.

### *Subject characterization*

Table I summarizes baseline demographic data, OA symptoms, and prior treatment for all patients eligible for effectiveness analysis. The two randomized groups were comparable at baseline, except for height, BMI, prior use of acupuncture, and steroid injections ($P$ values $< 0.05$). The mean age was approximately 61 years for both groups, with the majority being female, Caucasian, and overweight (BMI $> 29$). Nearly half of the participants were retirees. Both groups had been treated for OA of the knee for an average of 8 years. A greater proportion of patients in the control group had tried acupuncture and steroid injections than those in the test group.

Although not a criterion for study entry, eligibility of subjects was verified with the Kellgren–Lawrence scale, a method for measuring the presence and severity of OA. An independent facility and blinded physician scored all

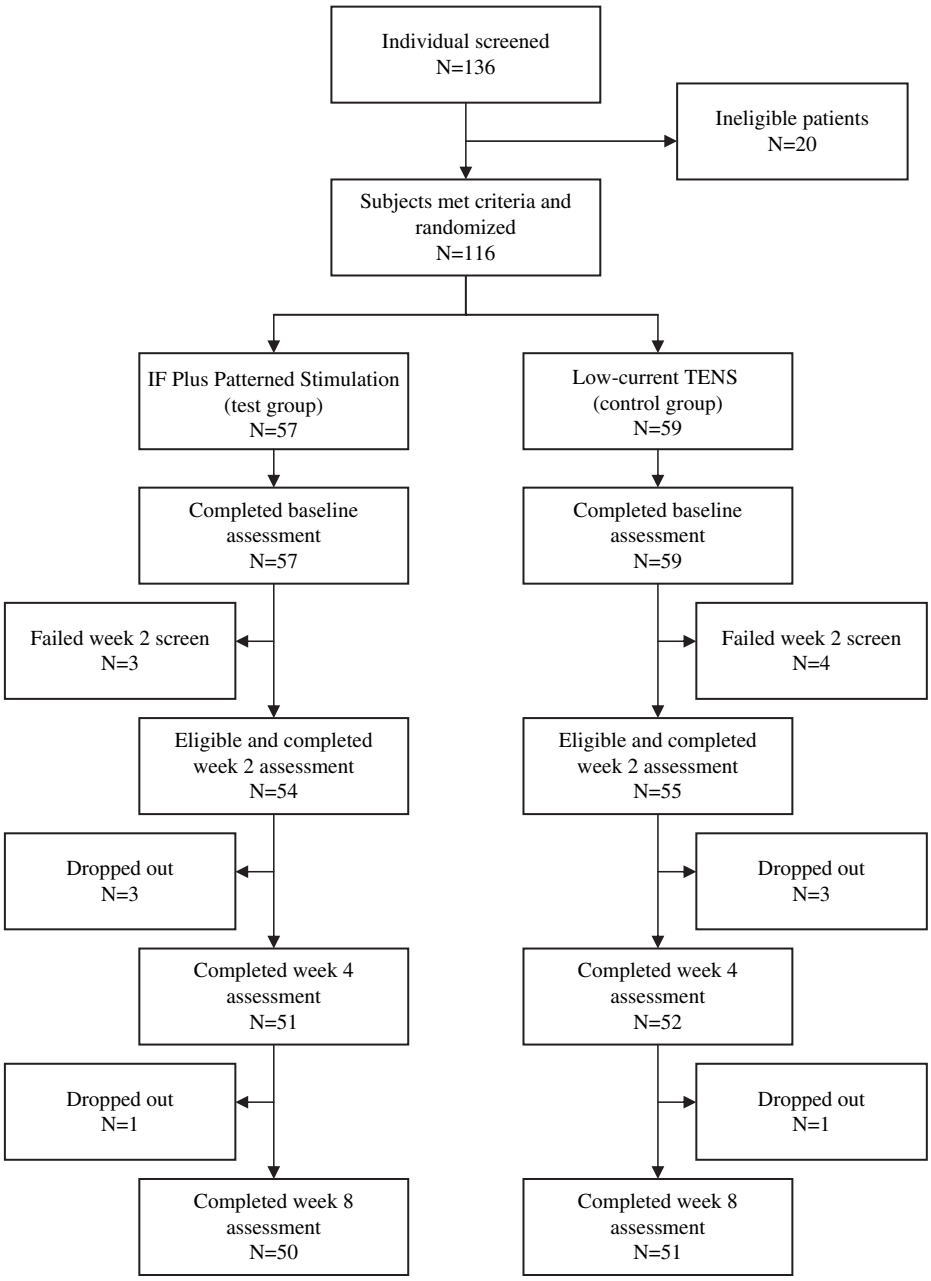


Fig. 1. Participants' progression.

available films taken at baseline for enrolled subjects. All subjects were determined to have a Kellgren–Lawrence score of at least 1 for OA of the knee. These scores were also analyzed for their impact on the statistical significance of the three WOMAC subscales. It was determined that there was no significant difference in the baseline Kellgren–Lawrence scores between treatment groups and that there was no statistical influence of these scores on the analysis of the WOMAC indices.

### WOMAC INDICES OF PAIN, FUNCTION AND STIFFNESS

Tables II–IV list the baseline mean and mean change from baseline to last visit for each of the WOMAC subscales. Lower scores are indicative of less impact of OA. The two treatment groups had comparable baseline means for each of the WOMAC subscales ($P$ values $> 0.5$). After 8 weeks of treatment, patients in the test group had significantly greater reduction than patients in the control group in the WOMAC pain subscale (3.98 vs 1.90; $P = 0.002$), physical function subscale (12.86 vs 6.74; $P = 0.003$), and stiffness subscale (1.53 vs 0.74; $P = 0.004$), suggesting that IF plus patterned muscle stimulation was more efficient than low-current TENS in relieving pain, increasing function and decreasing stiffness.

Stepwise regression analysis showed the four imbalanced baseline variables (height, BMI, prior use of acupuncture and steroid injections in Table I) had no impact

Table I
*Patient characterization*

| | Test group ($N=54$) | Control group ($N=55$) | $P$ value |
|---|---|---|---|
| Females: $N$ (%) | 36 (66.7%) | 43 (78.2%) | 0.18 |
| Age | | | |
| Mean ± SD | 62.6 ± 10.5 | 60.8 ± 11.4 | 0.37 |
| Range | 38–87 | 22–86 | |
| Weight (lb) | | | |
| Mean ± SD | 185.6 ± 39.1 | 193.1 ± 41.3 | 0.33 |
| Range | 112–288 | 114–298 | |
| Height (inch) | | | |
| Mean ± SD | 66.7 ± 3.2 | 65.4 ± 3.6 | 0.040 |
| Range | 60–74 | 58–74 | |
| BMI (kg/m$^2$) | | | |
| Mean ± SD | 29.3 ± 5.4 | 31.7 ± 5.8 | 0.025 |
| Range | 19.9–41.4 | 20.0–44.1 | |
| Race | | | |
| American Indian or Alaska native | 0 (0%) | 2 (3.6%) | 0.62* |
| African American | 1 (1.9%) | 2 (3.6%) | |
| Caucasian | 39 (72.2%) | 42 (76.4%) | |
| Asian | 0 (0%) | 2 (3.6%) | |
| Other | 14 (25.9%) | 7 (12.7%) | |
| Work status | | | |
| Full time | 12 (22.2%) | 12/54 (22.2%) | 0.97 |
| Part time | 10 (18.5%) | 9/54 (16.7%) | |
| Retired | 26 (48.2%) | 27/54 (50.0%) | |
| Unemployed | 5 (9.3%) | 4/54 (7.4%) | |
| Medical disability | 1 (1.9%) | 2/54 (3.7%) | |
| Knee treated† | | | |
| Left | 22/53 (41.5%) | 19/53 (35.9%) | 0.55 |
| Right | 31/53 (58.5%) | 34/53 (64.2%) | |
| Length of treatment (years) | | | |
| Mean ± SD | 8.0 ± 7.9 | 8.6 ± 7.8 | 0.73 |
| Range | 0–30 | 0–29 | |
| OA in other joints: $n$ (%) | 33 (61.1%) | 34 (61.8%) | 0.94 |
| Prior treatments for OA symptoms | | | |
| OTC analgesic | 50 (92.6%) | 52 (94.6%) | 0.72 |
| NSAIDs | 35 (64.8%) | 38 (69.1%) | 0.64 |
| Opioid | 27 (50.0%) | 20 (36.4%) | 0.15 |
| Oral steroid | 9 (16.7%) | 16 (29.1%) | 0.12 |
| Supplements | 37 (68.5%) | 42 (76.4%) | 0.36 |
| Vitamins | 37 (68.5%) | 46 (83.6%) | 0.06 |
| Physical therapy | 27 (50.0%) | 31 (56.4%) | 0.51 |
| Acupuncture | 4 (7.4%) | 17 (30.9%) | 0.002 |
| Steroid injection | 14 (25.9%) | 25 (45.5%) | 0.034 |

*Caucasian vs non-Caucasian.
†Patients with at least one post-baseline visit.

on the analysis of the two WOMAC primary outcomes (pain and function), and the difference between treatment groups remained statistically significant.

Four patients (two in each group) had missing values and were excluded from the primary effectiveness analyses of WOMAC pain and function. Two sensitivity analyses showed that neither inputting a value of zero nor the most conservative value (the worst score in the test group and the best score in the control group) as the change from baseline changed the statistical significance. This demonstrates that the loss of four patients due to missing values did not impact the results enough to compromise the conclusion of superiority of the test group over the control group in the WOMAC pain and function subscales.

Table II
*Mean baseline and change from baseline to the last visit in WOMAC pain subscale*

| | Test group ($N=52$) | Control group ($N=53$) |
|---|---|---|
| Baseline | | |
| Mean ± SD | 9.6 ± 3.3 | 9.3 ± 3.5 |
| Range | 2–18 | 2–18 |
| $P$ value | 0.61 | |
| Change from baseline* | | |
| Mean | −3.98 | −1.90 |
| Difference (98.75% CI) | 2.09 (0.60–3.57) | |
| $P$ value | 0.002 | |

*Adjusted for study center and baseline assessment.

Two secondary effectiveness analyses, which included only patients who completed the study, were performed for the WOMAC pain and function scale. The first analysis assessed the interaction of treatment group by time. The mean change from baseline to each scheduled visit for the two treatment groups were contrasted (Fig. 2). The results showed that at the week 2 visit, patients in the test group already had significantly greater reduction than the control group in WOMAC subscales of pain (2.50 vs 1.08; $P=0.008$) and function (7.74 vs 4.14; $P=0.03$), suggesting that the test group started to show a stronger beneficial effect after only 2 weeks of stimulation. The second analysis compared the frequency counts of patients who reported 20% or more improvement in two WOMAC primary outcomes. The results showed that a higher percentage of patients in the test group had improvement for WOMAC subscales of pain (71.2% vs 49.1%; $P=0.023$) and function (65.4% vs 45.3%; $P=0.030$) than patients in the control group. Therefore, the secondary effectiveness analyses result mirrored the primary analyses in favor of the test group.

### PAIN AND QUALITY OF LIFE VAS RATINGS

Tables V and VI list the baseline mean and mean change from baseline to last visit for the overall pain VAS and quality of life VAS. Lower scores indicated less pain or less impact of OA on quality of life. The two treatment groups had comparable baseline means for both VAS ratings.

Table III
*Mean baseline and change from baseline to the last visit in WOMAC function subscale*

| | Test group ($N=52$) | Control group ($N=53$) |
|---|---|---|
| Baseline | | |
| Mean ± SD | 32.8 ± 11.6 | 33.7 ± 12.6 |
| Range | 8–61 | 6–65 |
| $P$ value | 0.70 | |
| Change from baseline* | | |
| Mean | −12.86 | −6.74 |
| Difference (98.75% CI) | 6.12 (1.57–10.66) | |
| $P$ value | 0.003 | |

*Adjusted for study center and baseline assessment.

Table IV
*Mean baseline and change from baseline to the last visit in WOMAC stiffness subscale*

| | Test group ($N = 53$) | Control group ($N = 53$) |
|---|---|---|
| Baseline | | |
| Mean ± SD | 4.49 ± 1.25 | 4.51 ± 1.37 |
| Range | 2–7 | 2–8 |
| *P* value | 0.94 | |
| Change from baseline* | | |
| Mean | −1.53 | −0.74 |
| Difference (95% CI) | 0.80 (0.26–1.34) | |
| *P* value | 0.004 | |

*Adjusted for study center and baseline assessment.

The mean changes from baseline to last visit in quality of life VAS rating were similar between the two groups (18.17 vs 18.16; $P = 0.99$). Patients in the test group had a greater decrease in the overall pain VAS (27.91 vs 23.19; $P = 0.29$) at their last visit, but the difference between treatment groups did not achieve statistical significance. However, if only patients who completed the study (49 in test group and 50 in control group) were included for the analysis, the difference between groups in mean change from baseline increased from 4.71 to 9.40 for overall pain VAS rating and achieved statistical significance ($P = 0.038$).

Secondary effectiveness analyses for treatment group by time interaction or frequency counts of patients who achieved 20% or more improvement did not show statistical significance.

### ADHERENCE

Compliance with the treatment was assessed by the difference between the number of days each patient was in the study and the number of days that he/she used the device. This was only done for patients who completed the study. 94.1% of the 101 subjects who completed the study used the device on at least half of the days after the initial 2-week compliance screening period. Of the six non-compliant subjects (two from the test group and four in the control group), one (from the control group) did not use the device at all after the 2-week compliance screening period.

### USE OF BREAKTHROUGH MEDICATION

Use of breakthrough medication for pain was reported at week 4 and 8 assessments. Very few patients (one in the test group and five in the control group) used breakthrough medication for pain, and the results were comparable between the two treatment groups.

### SAFETY ANALYSIS

Adverse events categories included skin irritation, skin burns, muscle soreness, electrical shock, and unanticipated adverse events. Adverse events reported in this study were mild. The rate was low and very similar in the two treatment groups: there were five adverse events in the test group and nine adverse events in the control group. One of the adverse events (in the control group) was rated as probably related to the study device. The patient reported muscle soreness, which did not require treatment and was resolved after 1 day. The patient completed the study as planned.

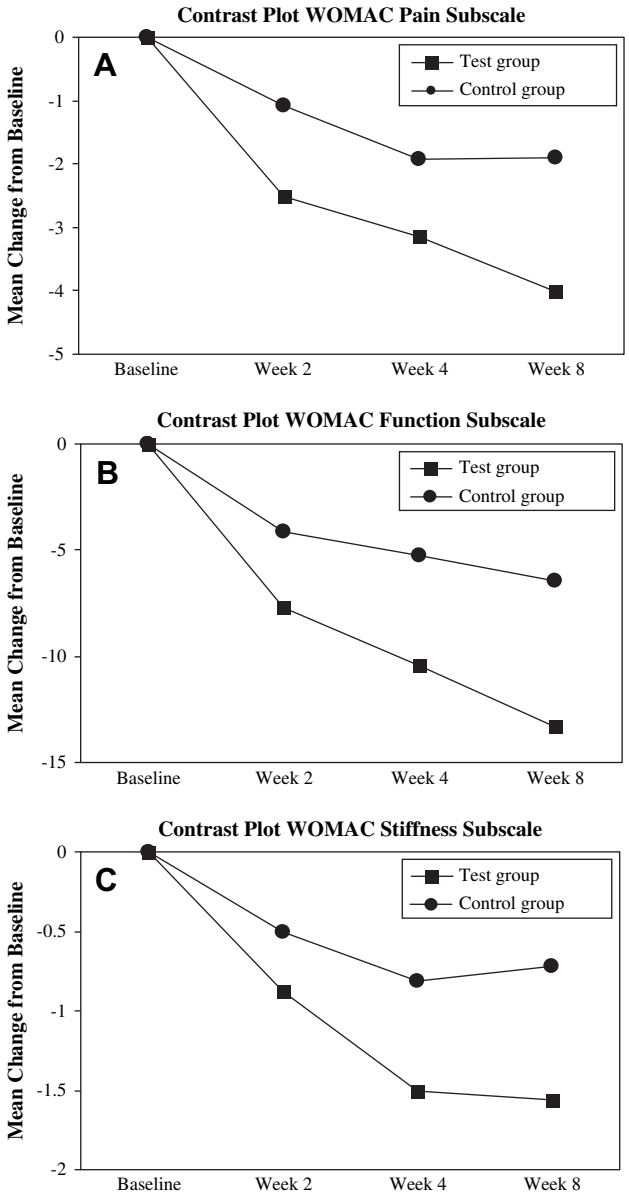


Fig. 2. Scores of WOMAC subscales of pain (A), function (B), and stiffness (C) at each scheduled visit.

## Discussion

The study assessed the benefits of a home-based electrostimulation treatment combining IF and patterned muscle stimulation in treatment of OA of the knee. Low-current TENS was applied as a control. WOMAC subscales of pain, stiffness, and function and VAS for overall pain and quality of life were measured at various points during the 8-week study. Patients treated with IF plus patterned stimulation reported decreases in pain and knee stiffness and increases in physical function at the end of the study. Improvement of the three WOMAC subscales in the test group was significantly greater than in the control group. We also observed that patterned stimulation started to show stronger effects in relieving pain and improving function than low-current TENS after only 2 weeks of treatment.

Table V
*Mean baseline and change from baseline to the last visit in overall pain VAS*

| | Test group ($N=53$) | Control group ($N=53$) |
|---|---|---|
| Baseline | | |
| Mean ± SD | 63.7 ± 13.2 | 60.7 ± 15.4 |
| Range | 30–86 | 11–100 |
| *P* value | 0.26 | |
| Change from baseline* | | |
| Mean | −27.91 | −23.19 |
| Difference (98.75% CI) | 4.71 (−5.37–14.80) | |
| *P* value | 0.29 | |

*Adjusted for study center and baseline assessment.

Patients treated with patterned stimulation also had a greater decrease in the VAS overall pain assessment at their last visit, although the difference did not achieve statistical significance. It was not expected that VAS overall pain and quality of life would achieve statistical significance, because they are tests for general purposes, while WOMAC is a test specifically designed for OA of the knee.

In our study, patients in the test group, who received IF plus patterned muscle stimulation, reported greater decreases in pain. Seventy percent of the patients in the test group had 20% or more reduction in the WOMAC pain subscale, and the patient percentage was significantly higher ($P=0.023$) than in the control group. After only 2 weeks of treatment, the test group already started to show this greater pain relief than the control group ($P=0.008$). These significant results may in part be due to IF stimulation. IF stimulation delivers current more deeply than conventional TENS[13,14]. In our study, IF stimulation was applied prior to patterned muscle stimulation, and this provided better pain management and allowed the underlying OA condition to be more comfortably treated with patterned muscle stimulation.

In addition to improvement on the pain subscale, patients in the test group had significantly greater improvement in the WOMAC physical function subscale ($P=0.003$) and stiffness subscale ($P=0.008$) than patients in the control group. The difference was perceived after only 2 weeks of treatment ($P=0.03$ for function). The improvement of function and stiffness was likely the result of patterned muscle stimulation, with a possible contribution from better pain management. Muscle stimulation excites motor neurons and causes a muscle contraction. The muscle stimulation used in this study was based on normally occurring nerve and muscle timing patterns and consisted of tri-phasic bursts of electrical impulses that were delivered in a timing configuration replicating electromyographic patterns of movement associated with agonist/antagonist pairs of muscles (the quadriceps and hamstrings) during a high-level running activity. Subjects adjusted stimulation intensity to a comfortable level that generated low-level contractions (stimulation amplitude was fixed at 60 mA, and subjects adjusted the stimulation intensity by varying pulse width). By using the same inter-muscular sequencing as the body's natural neurophysiological electrical impulses, patterned stimulation re-educated disused and weak muscles by facilitating normal movement. This should promote local blood circulation, increase range of motion and strength, prevent or retard disuse atrophy, and restore knee function[15–17].

Table VI
*Mean baseline and change from baseline to the last visit in quality of life VAS*

| | Test group ($N=52$) | Control group ($N=51$) |
|---|---|---|
| Baseline | | |
| Mean ± SD | 53.3 ± 24.1 | 57.8 ± 23.8 |
| Range | 0–95 | 16–100 |
| *P* value | 0.93 | |
| Change from baseline* | | |
| Mean | −18.17 | −18.16 |
| Difference (98.75% CI) | 0.01 (−9.32–9.35) | |
| *P* value | 0.99 | |

*Adjusted for study center and baseline assessment.

In this study, electrodes were placed on patients' vastus lateralis, vastus medialis, and hamstrings, as the primary functions of the quadriceps and hamstrings are knee extension (straightening the knee) and knee flexion (bringing the heel toward the buttocks). By contracting and exercising the muscles that mainly control knee movement, patterned stimulation can decrease knee stiffness and increase range of motion. It is the authors' opinion that, by mimicking the body's natural gait pattern, patterned stimulation improves the quality and viscosity of synovial fluid in the knee. Patterned stimulation is a neurofacilitative treatment that may correct the cumulative effects of pain-induced guarding. This proposed mechanism is supported by a study conducted in dogs with established OA in one of the two stifle joints to examine the effects of patterned stimulation on the quality and viscosity of synovial fluid. After 14 weeks of treatment with patterned stimulation, synovial fluid analysis revealed changes in synovial fluid markers, including a trend for decreasing sulfated glycosaminoglycan (sGAG), and a 20% decrease in soluble collagen within the synovium, compared to the control group (MS Shih, D.V.M., Ph.D., unpublished data, 2007). Durability of treatment in a carryover effect is unknown and warrants further study.

Our results were consistent with other published research that proved the therapeutic function of muscle stimulation in increasing muscle strength and improving functional performance. Delitto *et al.* compared electrical muscle stimulation vs voluntary exercise in strengthening thigh musculature after anterior cruciate ligament surgery[18]. Their results showed that patients in the electrical muscle stimulation group who finished the 3-week training regimen achieved higher percentages of both extension and flexion torque compared to patients in the voluntary exercise group. Durmus *et al.* tested the effects of electrical muscle stimulation on pain, disability, and quadriceps strength in older female patients with OA of the knee, with biofeedback-assisted isometric exercises as a control[19]. Their results showed that electrical muscle stimulation was as effective as voluntary exercise in improving pain, physical function, and stiffness scores after therapy. Talbot *et al.* tested the feasibility of neuromuscular stimulation to increase quadriceps femoris (QF) strength in older adults with symptomatic OA of the knee[20]. Their results showed that patients in neuromuscular stimulation plus education group had increased QF muscle strength, physical activity and function performance than patients in the education-only group.

Some pain relief was seen in the control group using low-current TENS, but the change was not as substantial as when using IF plus patterned stimulation. TENS has been used clinically to produce analgesia and anesthesia for acute or chronic pain relief[21]. However, unlike high-frequency IF stimulation, TENS cannot overcome the high

capacitive resistance of skin[22], and this limits its depth of penetration and efficacy in pain relief. We used 0.5 mA output, which was at the lower range of TENS and did not cause muscle contraction; hence, it was not expected that low-current TENS would generate the same curative effect on knee mobility and function as patterned stimulation.

The goals of treating OA of the knee are to control symptoms and to restore function. Our study showed that a two-step stimulation combining IF and patterned muscle stimulation in a single treatment appears to be a promising intervention for relieving pain, decreasing knee stiffness and improving function. To investigate further the effectiveness of this combination of stimulation for OA of the knee, future studies should follow subjects for several weeks or months after the end of treatment to evaluate the post-treatment durability of patterned stimulation. Future studies should also include kinematic evaluations to further evaluate the effect of patterned stimulation on functional walking capabilities. It would also be beneficial to compare the efficacy of patterned stimulation against controls based on other standard therapies, including physical therapy and pain medications. Our results suggest that patterned stimulation has the potential to be a more effective treatment modality than conventional single-step TENS for OA of the knee. Patterned stimulation treatment is a non-invasive, non-habit forming, cost-effective rehabilitative modality. It is ideal for patients who have painful OA conditions, stiff joints from disuse of muscles, or difficulty exercising.

## Conflict of interest

This study was supported by industrial funding. The sponsoring organization, RS Medical, has financial interest in patterned stimulation supplied by the RS-4i® electrostimulation device. The corresponding author, WJ Carroll, is employed by the sponsor as Vice President of Research and Product Development. J.J. Greenberg was employed by the sponsor as Research Scientist during the conduct of the study. F.X. Burch, M.D., of Radiant Research, San Antonio and J.N. Tarro, M.D., of Radiant Research, Portland were paid contributors (as principal investigators).

*Role of the Funding Source:* The sponsor of this study, RS Medical, designed the study and provided the infrastructure for collecting study data. RS Medical and its paid consultants analyzed and interpreted the data and prepared this manuscript. RS Medical is responsible for the decision to submit the manuscript for publication.

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